Egyptian Journal of Anaesthesia (2012) **28**, 37–42

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Lidocaine-tramadol versus lidocaine-dexmedetomidine for intravenous regional anesthesia

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Received 6 August 2011; accepted 15 August 2011
Available online 14 September 2011

KEYWORDS

Tramadol;
Dexmedetomidine;
Intravenous regional anesthesia

Abstract *Background:* Intravenous regional anesthesia (IVRA) has been used for more than a century. Both tramadol (synthetic opioid) and dexmedetomidine (α_2-agonist) can act locally.
Aim of the work: To compare effects of adding tramadol versus dexmedetomidine to lidocaine during IVRA.
Patients and methods: Sixty patients were randomly assigned into: Group C (n = 20), Group T (n = 20), and Group D (n = 20). All patients received 3 mg/kg 0.5% lidocaine [+100 mg tramadol in Group T, or 1 μg/kg dexmedetomidine in Group D]. Times of onset and offset of sensory and motor blocks, and time to tourniquet pain were recorded. Postoperative VAS score, time to first dose, and total amounts of supplementary analgesia (Paracetamol) were recorded. Sedation was evaluated using Ramsay sedation scale (RSS).
Results: Significantly shorter onset times and longer recovery times of sensory and motor block were recorded in Groups T and D compared to Group C ($P < 0.05$); while, with no significant differences between Groups T and D. Delayed onset of tourniquet pain occurred in Groups T and D compared to Group C ($P < 0.05$) with no significant differences between Groups T and D. Fourteen patients required fentanyl to control tourniquet pain in Group C compared to (5 and 4) in Groups T and D respectively. Significantly lower Postoperative VAS score, longer time to first dose and lower consumption of Paracetamol were recorded in Groups T and D than Group C; with no significant differences between Groups T and D. Complications were skin rash in 30% of patients in Group T, bradycardia and sedation in 35% and 65% of patients in Group D respectively.

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Peer review under responsibility of Egyptian Society of Anesthesiologists.
doi:10.1016/j.egja.2011.08.003

Conclusion: Addition of either tramadol or dexmedetomidine enhances lidocaine during IVRA with higher incidence of skin rash with tramadol and postoperative bradycardia and sedation with dexmedetomidine.

1. Introduction

Intravenous regional anesthesia (IVRA) is a technique that should be honored for playing a respected role in anesthesia for more than one hundred years. It was first performed by a German scientist named August Bier in 1908 (thereby, the technique was named after him as Bier's block) [1]. It has many advantages being a simple and easy technique, reliable with high success rate, and cost-effective [2]. Many researches have been aiming to overlap the disadvantages of this type of block including tourniquet pain and insufficient postoperative pain relief by using adjuvant drugs to potentiate local anesthetics such as tramadol [3], α_2-agonists [4], neostigmine [5], or non-steroidal anti-inflammatory drugs (NSAIDs) [6].

Tramadol is a centrally acting synthetic opioid that has been widely used. It has weak agonist actions at the μ-opioid receptor, releases serotonin, and inhibits the reuptake of norepinephrine [7,8].

Opioids possess local anesthetic properties *in vitro* [9] Despite that the use of morphine [10] and fentanyl [11] showed a limited role, yet, meperidine enhanced lidocaine in IVRA [12] and proved efficacy when even used alone [13].

Dexmedetomidine, is α_2-adrenoceptor agonist that has been the subject of many anesthetic researches owing to its sedative and analgesic effects [14]. It has a ratio of selectivity towards α_2/α_1 receptors of 1620:1 compared to 220:1 for clonidine. Therefore, is considered as a full agonist of the α_2 receptor (with more potent neurological and less cardiovascular effects) [15].

In the current study we aimed to compare the effects of tramadol versus dexmedetomidine when added to lidocaine during intravenous regional anesthesia.

2. Patients and methods

After approval of our committee and obtaining written consent from each patient;

Sixty patients of both sexes with American Society of Anesthesiologists (ASA) physical status I or II, aged between 20 and 50 years, who were scheduled for short procedure surgery of the hand or the forearm (ganglion excision, carpal tunnel syndrome, fractured radius, fractured finger, and hardware removal of forearm) in Zagazig University Surgical Hospital were included in this study. Exclusion criteria included: history of drug allergy, cardiac disease, hypertensive patients treated with α-methyldopa or clonidine, patients who were given any analgesia within the last 24 h, liver disease, kidney disease, or sickle cell anemia.

Patients were randomly assigned into three groups: Group C-patients received 3 mg/kg 0.5% lidocaine diluted with 0.9% normal saline to a total volume of 40 ml (n = 20), Group T-patients received 3 mg/kg 0.5% lidocaine + 100 mg tramadol (Tramal® 100 mg/2 ml; MINAPHARM under license of GRUNENTHAL, Germany) diluted with 0.9% normal saline to a total volume of 40 ml (n = 20) and Group D-patients received 3 mg/kg 0.5% lidocaine + 1 μg/kg dexmedetomidine (Precedex® 200 μg/2 ml; Abbott, North Chicago, IL) diluted with 0.9% normal saline to a total volume of 40 ml (n = 20).

Before starting the block with IVRA, two cannulae (20 gauge) were applied; one in dorsal vein of the hand near the site of surgery through which anesthetic drugs are to be given, and the other in opposite hand for intra-operative fluid transfusion.

Esmarch bandage was used for exsanguination of the operative arm, and a pneumatic tourniquet was placed around the upper arm. The proximal cuff was inflated to 250 mm Hg. The proper performance of the tourniquet was assured by inspection of the limb pallor, absence of radial pulse, and loss of pulse oximetry tracing of the ipsilateral index finger. After the bandage was removed, the prepared anesthetic solution was injected over 1 min in a double-blinded, randomized fashion by using a closed envelope system.

The sensory block was assessed every 30 s starting 2 min after injection until complete sensory block was established in the dermatomal sensory distribution of the ulnar, median, and radial nerves by a pinprick test using a 22-gauge short-beveled needle. Sensory loss was evaluated by testing dermatomal distribution of each nerve based on the hypothesis that "different nerve fibers have a varying susceptibility to blockade" [16] as follows: (1) ventral aspect of the forearm and first webspace (radial nerve); (2) thenar eminence and index finger (median nerve); (3) hypothenar eminence and little finger (ulnar nerve). Motor function was evaluated by asking the patient to flex and extend his wrist and fingers.

When sensory and motor block was ensured, the distal cuff was then inflated to 250 mm Hg followed by release of the proximal tourniquet. Surgical intervention was then allowed.

The visual analog scale (VAS) which was used to evaluate tourniquet pain (0 = no pain and 10 = worst pain imaginable) was recorded at the times of 5, 10, 15, 25, 35 and 45 min after tourniquet application. 1 μg/kg fentanyl was given for relieving tourniquet pain when VAS > 3. Time to complain of tourniquet pain was recorded for each patient (starting point: just after tourniquet inflation).

The tourniquet was not deflated before 40 min of local anesthetic injection and was not inflated more than 90 min.

At the end of surgery, the tourniquet deflation was performed by repeated inflation-deflation technique (the tourniquet was deflated three times for 10 s period followed by 1 min of reinflation). Time till regaining of sensation and motor power was recorded starting just after tourniquet release.

For all patients, mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO_2), and heart rate (HR) were monitored. Hypotension was considered if 30% decrease below baseline MAP occurred and was planned to be treated with IV ephedrine (6 mg bolus). Bradycardia was considered if $\geqslant$25% decrease from baseline value occurred and was

planned to be treated with IV atropine 1 mg. The decrease in arterial oxygen saturation <91% was treated with O_2 via a transparent face mask.

Postoperative analgesia was evaluated using VAS every 30 min after tourniquet deflation for 2 h in postanesthesia care unit (PACU) with the highest value of VAS for each patient considered as postoperative VAS score. During the first 24 h after surgery, the time to first dose of supplementary analgesia was recorded to each patient starting just after tourniquet deflation [patients received IV Paracetamol (Perfalgan) 1 g when VAS was >3], and total amounts of Paracetamol administered to each group were recorded.

Patients' degree of sedation was evaluated using Ramsay sedation scale (RSS) [17] at 5, 10, 15, 25, 35 and 45 min after tourniquet deflation with the highest value of RSS for each patient considered as postoperative RSS score. RSS has six different levels:

1. Patient is anxious and/or agitated.
2. Patient is cooperative, oriented and tranquil.
3. Patient responds to commands only.
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6. Patient exhibits no response.

2.1. Statistical analysis

It is clinical trial study, thus, sample size was calculated ($n = 60$) by using pilot study to determine patients scheduled for IVRA in one month then the whole patients (whole population) for one year was calculated. Systematic random sample technique was used for allocation of the three study groups. Power of the study was 80%, confidence interval was 95%, level of significance was determined at 5% ($P < 0.05$), and expected non compliance (non-response rate) 20% was also considered.

Data were checked, entered and analyzed using SPSS version 11. Data were expressed as mean ± standard deviation (SD) for parametric results. Qualitative data were expressed as number. ANOVA, paired *t*-test, chi-square (χ^2) or Krunskal–Wallis test were used when appropriate. $P < 0.05$ was considered significant.

3. Results

There were no significant differences among groups for demograghic data and total tourniquet time (Table 1).

Sensory as well as motor block onset times (block performance) were significantly shorter in Groups T and D compared to Group C ($P < 0.05$), with no significant differences between tramadol and dexmedetomidine groups. Sensory and motor block recovery times were significantly longer in Groups T and D when compared to Group *C* ($P < 0.05$). But no significant differences between tramadol and dexmedetomidine groups [suggesting the equipotent adjuvant effect of tramadol and dexmedetomidine when added to the lidocaine] (Table 2).

Tourniquet pain onset time was significantly longer in Groups T and D than in Group C ($P < 0.05$) with no significant differences between tramadol and dexmedetomidine groups. The numbers of patients who required fentanyl were 14 in Group C, 5 in Group T, and 4 in Group D with significantly higher number in Group C compared to Groups T and D (Table 2).

Postoperative VAS score in Groups T and D compared to Group C were significantly lower ($P < 0.001$), while it was comparable between both groups (T and D). Time to first dose of supplementary analgesia (Paracetamol) was significantly longer in Groups T and D compared to Group C, with no significant differences between tramadol and dexmedetomidine groups. The postoperative analgesic consumption in the first 24 h was significantly lower in Group T and Group D than Group C ($P < 0.001$), with no significant differences between tramadol and dexmedetomidine groups (Table 2).

As shown in Table 3, six of the patients (30%) in Group T developed skin rash without itching within the first 5 min after injection of tramadol–lidocaine solution, below the tourniquet level and it subsided spontaneously by the end of surgery [compared to no patients (0%) in Groups D and C]. Seven patients (35%) developed bradycardia just after tourniquet deflation in Group D compared to no patients (0%) in Groups T and C. This decrease in heart rate was accompanied by insignificant decrease in blood pressure and all of them responded to 1 mg IV atropine (although patients in Group D recorded lower levels of blood pressure after tourniquet deflation, the results were statistically insignificant when compared to those recorded in Groups C and T). Ramsay sedation score was significantly higher (RSS = 2) in 13 patients (65%) in Group D compared to Groups C and T during the first 30 min after release of tourniquet. None of the patients in any group developed hypotension or hypoxemia during surgery or during the first 24 h postoperatively.

4. Discussion

The current study revealed that addition of either tramadol or dexmedetomidine to lidocaine for IVRA was accompanied by more rapid onset and delayed offset of sensory and motor

Table 1 Demographic data, and time of tourniquet pain.

	Group C ($n = 20$)	Group T ($n = 20$)	Group D ($n = 20$)
Age (years)	36.0 ± 14.8	35.7 ± 14.2	38.2 ± 11.7
Gender (M/F)	10/10	11/9	11/9
Weight (kg)	75.2 ± 5.9	74.6 ± 3.6	74.7 ± 7.8
Surgical duration (min)	46.8 ± 16.9	44.0 ± 22.1	42.9 ± 25.1
Time of tourniquet application (min)	60.2 ± 14.5	57.3 ± 13.3	57.1 ± 14.0

Data were expressed as mean (±SD) as number.

Table 2 Performance of intra-operative anesthesia and postoperative analgesia of different agents used in the study.

	Group C (n = 20)	Group T (n = 20)	Group D (n = 20)
Sensory block			
Onset time (min)	3.6 ± 1.8	2.2 ± 1.2*	2.0 ± 1.7*
Recovery time (min)	3.2 ± 2.0	8.1 ± 1.1†	9.6 ± 0.7†
Motor block			
Onset time (min)	7.2 ± 1.3	4.5 ± 2.1*	3.9 ± 2.3*
Recovery time (min)	3.7 ± 3.1	9.4 ± 2.1†	10.2 ± 1.3†
First time to complain of tourniquet pain (min)	25.1 ± 2.3	33.9 ± 8.9†	34.2 ± 5.9†
Number of patients who needed fentanyl (VAS > 3)	14	5*	4*
Postoperative VAS scores	3.9 ± 2.6	2.2 ± 1.7*	1.8 ± 1.3*
Time to first dose of postoperative supplementary analgesia (Paracetamol) (min)	119.1 ± 12.3	242.4 ± 9.6†	269.9 ± 9.1†
Total dose of consumption of Paracetamol (g) in the first 24 h	2.44 ± 0.6	1.20 ± 0.1*	1.1 ± 0.3*

Data were expressed as mean (±SD) number.
* Significantly less compared to Group C ($P < 0.05$).
† Significantly more compared to Group C ($P < 0.05$).

Table 3 Incidence of complications between the three groups.

	Group C (n = 20)	Group T (n = 20)	Group D (n = 20)
Skin rash within the first 5 min	0	6 (30%)*	0
Bradycardia just after tourniquet deflation	0	0	7 (35%)*
Ramsay sedation score of [RSS = 2] during the first 30 min	0	0	13 (65%)*

Data were expressed as number or percent.
* $P < 0.05$ considered significant.

block, less severe and delayed onset tourniquet pain, delayed onset of postoperative pain, and less postoperative consumption of supplementary analgesia. Tramadol was accompanied with higher incidence of skin rash that subsided spontaneously, while, dexmedetomidine was accompanied by higher incidence of bradycardia at time of release of tourniquet, and sedation during the next 30 min.

Some studies have shown that tramadol has a local anesthetic action but the exact mechanism is still unknown [18]. Tramadol is related to codeine in its structure [19] and is selective for the mu-receptors [7] but the action on opioid receptors does not explain its local effect [20]. Moreover, fentanyl when added to local anesthetic for IVRA [21] did not has an adjuvant effect supporting the hypothesis of absent peripheral opioid-mediated mechanism during IVRA.

In a study by Acalovschi and coworkers [16] 100 mg tramadol enhanced the local anesthetic effect when added to 0.5% lidocaine for IVRA. This was in accordance with the results obtained in the present study. In their study, there were no effect for tramadol on motor block and they explained that by the small concentration of tramadol solution. However, the results obtained by Kapral and coworkers [20] showed prolonged motor block of the brachial plexus when same concentration of tramadol was added to mepivacaine for axillary brachial plexus block. The results of the current study came in accordance with the results obtained by Kapral and his colleagues regarding the effect of tramadol on motor block [20].

α_2-Adrenergic receptors that are present at nerve endings plays a role in pain modulation and some drugs perform their analgesic functions by preventing norepinephrine release at these receptors [22].

Tramadol can block the reuptake of the norepinephrine and 5-hydroxy-tryptamine at the α_2*adrenergic receptors [23]. Thereby, tramadol has an action similar to that of clonidine α_2-agonists, which inhibits the release of norepinephrine from α_2-adrenoceptors agonists [24].

Clonidine depresses nerve action potential by a mechanism other than its effect on α_2-adrenergic receptors which may account for perineural adjuvant effect to local anesthetics [25]. Adding clonidine to local anesthetics during IVRA revealed controversial results. Kleinschmidt and coworkers [26] found that clonidine did not add to the pattern of postoperative analgesia, while, Reuben and coworkers [27] found that clonidine made postoperative analgesia better. DEX is more selective to α_2-adrenoceptors than clonidine [15]. Thus, we thought that addition of DEX to lidocaine will not be associated with such debate. However, the patient safety was our target. Jaakola [28] was also interested in both efficacy and safety of IV dexmedetomidine and he used it as a premedication before IVRA. The results of that study revealed that 1 μ/kg dexmedetomidine produced desirable sedation, attenuated sympathoadrenal responses, and decreased opioid analgesic requirements but it did not prevent tourniquet pain.

Tourniquet pain is a major problem that comes after the use of a pneumatic tourniquet during surgical procedures involving the upper or lower limb. The mechanism by which tourniquet pain is elicited is yet unclear [29]. Many studies [4,30,31], have shown that using clonidine during IVRA decreased tourniquet pain. Clonidine has approximately 1/8 the potency Dexmedetomidine [14]. In the study by Memis and his colleagues [32], tourniquet pain was attenuated and total fentanyl consumption was reduced by adding dexmedetomidine to lidocaine solution

during IVRA. This was in accordance with the results obtained in the present study.

A major concern while using either tramadol or DEX as adjuvants to local anesthetics is the possibility of subsequent complications. In the current study, 30% of the patients in tramadol group experienced skin rash distal to the tourniquet, implying histamine release. This complication was also encountered in the study by Acalovschi and his colleagues [16].

Abrupt IV introduction of 0.5–2 μg/kg dexmedetomidine results in moderate hypotension, bradycardia, and sedation [33]. In his study, Memis and his colleagues [32] found that the addition of 0.5 μg/kg dexmedetomidine to lidocaine for IVRA enhanced the anesthetic and postoperative analgesic effect of lidocaine with cardiovascular stability during intra- and postoperative times. In the current study, bradycardia was detected in 35% of patients after release of tourniquet which might be explained by the higher dose of dexmedetomidine (1 μg/kg). The bradycardia observed in Group D was accompanied by insignificant decrease in blood pressure and might be attributed to sympathetic inhibition and decreased levels of circulating catecholamines caused by dexmedetomidine [14].

In the study by Memis and his colleagues [32], no sedation was detected with the use of 0.5 μg/kg dexmedetomidine for IVRA during intra-operative or postoperative period. This was not in agreement with the results obtained in the current study where Ramsay sedation score was significantly higher after tourniquet deflation in dexmedetomidine group and lasted for 30 min after which mat be attributed to the higher dose of dexmedetomidine used (1 μg/kg). Our results agreed with the results obtained by another study [34] which showed that even small doses of α_2-adrenergic agonists produce sedation.

5. Recommendations

According to the results obtained in the current study, either tramadol or dexmedetomidine can be used as an adjuvant to lidocaine during IVRA taking into considerations the possibility of relevant complications.

6. Conclusion

Either 100 mg tramadol or 1 μg/kg dexmedetomidine equipotently improves the performance of lidocaine when used during IVRA with higher incidence of localized skin rash with tramadol and higher incidence of postoperative bradycardia and sedation with dexmedetomidine.

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